REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing claim amendments and following comments.

I. Status of the Claims

Claims 4, 5, 9-15, 17, 53, 54, 58-63, 73-86, and 89 were cancelled previously. Claims 7, 8, 16, 18-25, 33, 34, 36-49, 56, 57, 64, 68-72, 87, 88, 90-100, 104 and 105 are cancelled in this response, without prejudice or disclaimer thereof. Claims 1, 26, and 50 have been amended with exemplary support in original claims 7 and 8. Claims 3, 32, 35, and 52 have been amended to be consistent with the base claims. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-3, 6, 26-32, 35, 50-52, 55, 65-67, and 101-103 will be pending, with claims 26-32, and 35 withdrawn from consideration.

II. Rejection of Claims under 35 U.S.C. §112, ¶2

Claim 105 is rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Without acquiescing to the ground for rejection, claim 105 is cancelled for the sole purpose of advancing the prosecution of the present application, thereby mooting the rejection.

III. Rejection of Claims under 35 U.S.C. §103(a)

A. Struengmann and Liversidge

Claims 1-3, 6-8, 16, 50-52, 55-57, 64-67, 87, 88, 90-97, 101, 104 and 105 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over PCT Publication No. WO 99/09988 by Struengmann et al. ("Struengmann") in view of PCT Publication No. WO 93/25190 by Liversidge et al. ("Liversidge"). Claims 7, 8, 16, 56, 57, 64, 87, 88, 90-97, 104, and 105 are cancelled. Applicants respectfully traverse the rejection of the remaining claims.

According to the Examiner, it would have been obvious to modify the micronized meloxicam composition taught by Struengmann in view of Liversidge's teaching of a nanoparticulate NSAID composition. The Examiner asserts that "one of ordinary skill in the art would have been motivated to, by routine experiment[,] optimize the particle size with the expectation of at least similar results . . . because it is known in the art to reduce particle size of a drug to obtain a higher bioavailability of said drug." Office Action, the paragraph bridging pages 3 and 4.

(1) The Examiner has failed to established a *prima facie* case of obviousness in view of the unpredictability in the art, as demonstrated by the accompanying Declaration of Dr. Gary G. Liversidge.

The Examiner's rejection rationale is based on the unsupported presumptions that: (i) all active agents can be made into stable nanoparticulate active agent compositions; and (ii) all nanoparticulate active agent compositions demonstrate improved bioavailability in comparison to the same active agent in the microparticulate form. These presumptions are incorrect, as detailed in the accompanying Declaration under 37 C.F.R. 1.132 executed by Dr. Gary Liversidge ("the Liversidge Declaration II"). Specifically, the Liversdige Declaration II attests to the facts that: (a) not all active agents can be made into stable nanoparticulate active agent compositions; and (b) not all nanoparticulate active agent compositions can achieve improved bioavailability.

More particularly, the Liversidge Declaration II teaches that even when a functional equivalent was successfully made into a nanoparticulate active agent formulation, another active agent in the same functional group could not be obtained. *See* the Liversidge Declaration II, ¶¶ 4-16. Moreover, the Liversidge Declaration II also teaches that certain active agents, such as orlistat, cannot be made into stable nanoparticulate active agent compositions despite numerous attempts. *Id.*, ¶¶ 17-20.

Furthermore, the Liversidge Declaration II teaches that even if a nanoparticulate active agent composition can be made, there is a lack of predictability regarding whether the nanoparticulate active agent composition will result in improved bioavailability of the component active agent. *Id.*, ¶¶ 25-28.

Accordingly, the Liversidge Declaration II provides data and analysis refuting the Examiner's incorrect presumptions regarding the predictability of making nanoparticulate active agent compositions as well as predicting the properties of such nanoparticulate active agent compositions.

(2) The combined teachings of the cited references fail to meet all claim limitations.

The claimed invention is directed to a pharmaceutical dosage form suitable for intravenous injection comprising a specific active agent, meloxicam, having an effective average particle size of less than 200 nm, in combination with specific surface stabilizers of polyvinylpyrrolidone and sodium dexoycholate or a combination thereof. The active agent and the surface stabilizers are in specifically prescribed amount.

The meloxicam particle size of the claimed dosage form is sufficiently small for intravenous injection. This is significant because a dosage form having a larger meloxicam particle size may cause adverse reactions when administered intravenously. Moreover, the meloxicam particle size of the claimed dosage form is sufficiently small for filter sterilization by passing through a 0.22 micron filter. This is significant as in general, a formulation suitable for intravenous injection must be sterilized before administration to patients. The claimed invention has the significant advantages of providing a low cost, filter sterilization option for a meloxicam dosage form suitable for intravenous injection.

In contrast, the combined teachings of the cited references fail to teach the small meloxicam particle size of less than 200 nm in combination with a dosage form for intravenous

injection. Furthermore, the cited references disclose a laundry list of surface stabilizers but fail to identify the specific surface stabilizers of the claimed invention as being preferred to other options. Therefore, in the absence of any teachings from the cited art, the Examiner has failed to articulate why the skilled artisan would have selected Applicants' claimed dosage form for intravenous injection, and the claimed specific surface stabilizers, for the nanoparticulate meloxicam composition. The Examiner could have only reached her rejection based on impermissible hindsight, informed by Applicants' own invention.

(3) The claimed invention is non-obvious in view of the unexpected results.

As demonstrated by the Liversidge Declaration II, all commercial meloxicam formulations approved by the FDA are in oral dosage forms (tablet or oral suspension). *See* ¶29. The oral dosage forms of meloxicam have the undesired side effect of gastrointestinal irritation. In fact, this side effect associated with the oral dosage form is so serious that the FDA requires the package label of meloxicam to carry a black box warning. *Id.*, ¶30. Additionally, an intravenous dosage form having fast onset is highly desirable, particularly for a pain reliever such as meloxicam, and particularly for a very young patient population. *Id.*, ¶32 and 38. Therefore, there was a need to develop an injectable formulation of meloxicam. *Id.*, ¶31.

However, it was difficult to obtain an intravenous meloxicam dosage form because meloxicam is poorly water soluble and a formulation containing large meloxicam particles is not suitable for intravenous injection. It was surprising that the claimed invention achieved the unexpected results of obtaining an intravenous nanoparticulate meloxicam formulation, which achieves the same or improved plasma concentration of meloxicam but in a much shorter time period in comparison to the commercial oral dosage form of meloxicam. *Id.*, ¶¶33-38. This is not taught or suggested by the cited art. As such, withdrawal of this ground for rejection is respectfully requested.

B. Struengmann, Liversidge and Desai or Courteille

Claims 18-25, 68-72 and 98-100 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Struengmann in view of Liversidge and PCT Publication No. WO 01/45706 by Desai et al. ("Desai") or U.S. Patent No. 5,384,124 to Courteille et al. ("Courteille"). Without acquiescing to the ground for rejection, the claims at issue are cancelled for the sole purpose of advancing the prosecution of this application, thereby mooting the rejection.

C. Struengmann, Liversidge and Cunningham

Claims 1-3, 6-8, 16, 50-52, 55-57, 64-67, 87, 88, 90-97 and 101-105 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Struengmann in view of Liversidge and U.S. Patent Application Publication No. 2004/0018242 by Cunningham et al. ("Cunningham"). Claims 7, 8, 16, 56, 57, 64, 87, 88, 90-97, 104, and 105 are cancelled. Applicants respectfully traverse the rejection of the remaining claims.

The teachings of Struengmann and Liversidge are discussed *supra*. Cunningham is cited for the alleged teaching of using sodium deoxycholate as a surface stabilizer for the claimed nanoparticulate meloxicam composition. However, the Examiner has failed to articulate why the skilled artisan would have included sodium deoxycholate as a surface stabilizer in view of Cunningham's teaching that sodium deoxycholate is used as a surface stabilizer for a nanoparticulate nystatin composition.

Specifically, nystatin is a polyene antimycotic useful in treating fungal infection. As disclosed by Cunningham, some "novel surface stabilizers . . . were selected [for the nanoparticulate nystatin composition] based on their potential bioadhesive or antimicrobial properties." *See* page 14, paragraph [0178]. In other words, one skilled in the art would have understood that the selection of these surface stabilizers was tailored to the specific active agent, nystatin. Cunningham further discloses that sodium deoxycholate was selected due to its unique property, i.e., "used as solubilizer in polyene formulations." *Id.*, Table 2.

In contrast, meloxicam of the claimed invention is an entirely different active agent from nystatin. The Examiner has failed to articulate why sodium deoxycholate would have been selected as a surface stabilizer for meloxicam, an active agent that is NOT a polyene, when Cunningham discloses the use of sodium deoxycholate as a solubilizer in polyene formulations.

Additionally, Example 4 of Cunningham demonstrates that sodium deoxycholate may have an adverse effect on the minimum inhibitory concentration (MIC) of a nanoparticulate nystatin composition using sodium deoxycholate as a surface stabilizer in comparison to other nanoparticulate nystatin compositions using other surface stabilizers. *See* page 15, paragraph [0189] ("with the exception of the Na Deoxycholate-stabilized sample of nanoparticulate nystatin, none of the milled formulations exhibited any significant differences in MIC, and surprisingly, were more active than unmilled nystatin material.") As such, the skilled artisan would have understood that there was some uncertainty regarding the effectiveness of a nanoparticulate nystatin composition comprising sodium deoxycholate as a surface stabilizer, as the use of a sodium deoxycholate was found to potentially adversely affect the MIC of the nanoparticulate nystatin composition.

In light of the specific purpose for the use of sodium deoxycholate for a nanoparticulate nystatin composition, and some uncertainty concerning the MIC of the formulation associated with sodium deoxycholate, the Examiner has not established a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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